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08/959,160	10/28/97	BALDWIN A	5470-140

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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 08/959,160	Applicant(s) Baldwin et al.
	Examiner Terry A. McKelvey	Group Art Unit 1636

☒ Responsive to communication(s) filed on *4/13/99* .

☒ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-12 and 14-28* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-12 and 14-28* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-12 and 14-28 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This rejection is maintained for reasons of record set forth in Paper No. 7, mailed 12/22/98 (repeated below and extended to new claims as necessitated by the applicant's amendment filed 4/13/99). Applicants' arguments and the Declaration both filed 4/13/99 have been fully considered but they are not deemed to be persuasive.

The claimed invention is drawn to a method of enhancing the cytotoxic effects of an antineoplastic chemotherapeutic agent or TNFa, by administering to a subject a therapeutically effective amount of an NF-kB inhibitor in conjunction with the agent of

TNFa. The claimed invention is also drawn to a method of treating a tumor with a chemotherapeutic agent (or treating a subject receiving a chemotherapeutic agent), the improvement comprising an effective amount of an NF-kB inhibitor with the therapeutic agent, increasing the cytotoxic effect of the agent. The chemotherapeutic agent is limited to daunorubicin, vincristine, and irinotecan in some claims, and, in other claims, the NF-kB inhibitor is limited to various different classes of inhibitors, such as super-repressor IkBa, NF-kB inhibiting proteasome inhibitors, ubiquitin inhibitors, proteasome peptidases, proteases, and antisense oligonucleotides that bind to mRNA encoding NF-kB (a broad range of very different compounds, having very different biochemistries). Thus, the claimed invention is drawn to in vivo therapy comprising administering an antineoplastic chemotherapeutic agent known in the prior art along with an NF-kB inhibitor, few, if any of which have been used in vivo to treat cancer. The only disclosed use for the claimed methods is for treatment of cancer, including any type of cancer from a very large list of cancers set forth in the specification at page 16, paragraph 3.

The nature of the invention is very complex because it is a method to be used to treat cancer, which is a very complex, hard to treat group of diseases. Cancer therapy is well-recognized in the art to be highly unpredictable. See Krontiris which teaches

that the various types of cancers have different causative agents, involve different cellular mechanisms, and, consequently, differ in treatment protocol. Although there exists some treatments for some specific cancers, there are no general treatments taught in the prior art based upon administration of an antineoplastic inhibitor chemotherapeutic agent with a drug chosen because it is an NF-kB inhibitor.

Neither the art nor the specification teaches a working example of administration of an antineoplastic chemotherapeutic agent in conjunction with a specific NF-kB inhibitor to a patient resulting in successful treatment of cancer.

There is no specific guidance in the prior art and only slight, prophetic generic guidance in the specification concerning how to use the claimed method to treat cancer. The

The two basic types of NF-kB inhibitors that the specification addresses: (1) vector or nucleic acid based inhibitors such as gene therapy accomplished by transfecting a cell to be treated with a nucleic acid encoding an NF-kB inhibitor, and transfection of antisense oligonucleotides that inhibit NF-kB RNA; and (2) other compounds that inhibit NF-kB (including both smaller molecules and larger ones such as proteins).

The special considerations with gene therapy are dealt with below. The considerations for the second type of inhibitor also are relevant for gene therapy and antisense therapy.

The specification merely teaches to use an administration method by "any suitable means", as would be apparent to one skilled in the art and briefly mentions some general administration routes and sites that are to be considered for any type of drug administration. General methods of preparing pharmaceutical compositions comprising the two types of drugs to be administered are also taught, along with general possible dosage ranges. The intended patients are taught as being of a very broad class: any humans or animals that suffer from essentially any type of cancer. The specification repeatedly teaches that the particular method used varies depending on the specific agent. However, very significantly, the neither the art nor the specification teaches specific parameters of treatment that have been shown to successfully function for specific NF-kB inhibitors in vivo to treat any disease, let alone cancer. The overall guidance provided is extremely slight because it can be considered to be merely speculative because the effective use of a compound having in vitro biological activity as a drug to treat a disease is extremely unpredictable as taught in the prior art by references such as Caldwell.

Caldwell is cited to show the unpredictability in the art concerning how to make and use a drug. Caldwell teaches that drug action is the result of interaction with target sites, for both desired and undesired actions, modulated by the transfer processes, the pharmacokinetic variables of absorption, distribution, metabolism and elimination, by which the drug enters and leaves the body. This reference teaches that there is far more inter- and intraspecies variation, in animals and humans, in the factors influencing the nature and extent of internal exposure, than in the sensitivity of drug targets and this pharmacokinetic variability is the cause of major problems in drug development. Caldwell also teaches that failure to take these pharmacokinetic defects, including poor absorption, very short or very long half-life, enzyme induction and high first pass effect, into consideration can cause expensive delay and/or failure during development. This reference thus shows that drug development is very unpredictable, requiring the consideration of many unpredictable factors in determining how to make and use the drug.

Gibbs et al also teaches that "unfortunately, the translation of modern molecular biology concepts into practical cancer therapeutics has proven to be far more problematic than first anticipated, and few true breakthrough agents have been found that significantly improve the survival of most cancer

patients. A partial explanation for these difficulties lies in understanding the fundamental process of drug discovery and the nature of pharmaceutically useful molecular targets (abstract). This reference also teaches that the existing biological assays are poorly predictive of the clinical efficacy of novel anticancer agents, and that the "take-home" lesson for researchers intent on finding the "cure" for cancer is not that practical intervention is improbable but rather that drug discovery is always difficult (page 197, column 1).

Simply stated, cancer therapy is very empirical. Successful treatments are based upon an extremely large amount of unpredictable trial and error experimentation.

The specification shows that expression of a super-repressor IkBa blocks TNF-stimulated NF-kB nuclear translocation in vitro, enhancing TNF-mediated apoptosis. The specification also shows that proteasome inhibitors enhance TNF apoptosis in vitro, that two types of chemotherapeutic agents, ionizing radiation, and daunorubicin induce nuclear translocation of NF-kB in vitro, and that over expression of the super-repressor enhanced cell killing by the two agents. Finally, the only in vivo data is from an animal model in which an adenoviral vector expressing the super-repressor IkBa is injected into nude mice with experimentally induced fibrosarcomas, along with a chemotherapeutic agent, which resulted in greater reduction of the tumors compared to the

chemotherapeutic agent alone. This data, although it shows that co-administration of the two types of agents for treatment of cancer might have promising biological activity against cancer, it by no means predictably teaches how to predictably use the promising in vitro biological activity (based upon only several different combinations of agents) in an in vivo administration method, as shown by the references described above. The only specific in vivo method taught is based upon one gene therapy method using a nude mice/experimentally induced cancer model. However, nude mice/cancer models are taught by Gura as being very unpredictive for cancer drug discovery. This reference teaches that the fundamental problem in drug discovery for cancer is that the model systems are not predictive at all. It is taught that the animals do not handle the drugs exactly as the human body handles them. This reference specifically teaches that xenograft screening based upon mice with impaired immune systems transplanted with human tumors (the nude mice/tumor model which is the only working example of an in vivo method of the claimed invention taught by the specification, falls into this category) turned out not to be much better than those obtained with the original models, mainly because the xenograft tumors don't behave like naturally occurring tumors in humans. This shows that results obtained with the in vivo animal model cannot be predictably applied to normal cancer in vivo.

The in vivo model taught in the specification, which is shown by the cited prior art as being very unpredictive for therapy, involves treatment of an organism using in vivo gene therapy. However, the specification fails to adequately teach how to perform gene therapy using the claimed method and vector. Gene therapy is a highly unpredictable and undeveloped field and the skill in the art is high. See Orkin et al which states (page 1):

"2. While the expectations and the promise of gene therapy are great, clinical efficacy has not been definitely demonstrated at this time in any gene therapy protocol, despite anecdotal claims of successful therapy and the initiation of more than 100 Recombinant DNA Advisory Committee (RAC)-approved protocols.

3. Significant problems remain in all basic aspects of gene therapy. Major difficulties at the basic level include shortcomings in all current gene transfer vectors and an inadequate understanding of the biological interaction of these vectors with the host."

The specification generally discloses some of the intended patients, amounts of the vector to be administered, what amount is considered to be therapeutically effective, the route and time course of administration, the sites of administration, the intended therapeutic product, the intended disease, and the intended target organs. However, this guidance is not

significant because it can be considered to be merely speculative because neither the art nor the specification teaches or provides specific guidance to teachings that show that, using the general methods referred to in the specification, a sufficient amount of the NF-kB inhibitor gene can be transferred into cells in vivo and expressed so as to have significant pharmacological effect and that this effect when it occurs in vivo acts to significantly treat cancer. The fact that some general methods referred to in the specification have, with a different gene, been able to get some measure of expression in vivo is in no way predictive that another, unrelated gene like an NF-kB inhibitor gene, can also be expressed to a similar level, and, importantly, be sufficient to treat cancer. There is simply no showing in either the art or the specification that one of skill in the art would be able to use the teachings of the art or the specification to predictably treat cancer using the claimed method in vivo, without much undue experimentation given the nature of the invention and the state of the gene therapy art. Thus, it is not credible, given the consensus scientific opinion concerning the gene therapy art, that one of skill could follow the teachings of the specification and be able to treat cancer using the claimed method without much undue experimentation. The consensus scientific opinion is that gene therapy was and still is highly unpredictable as evidenced by Orkin et al. The teachings of Verma et al, two years after

the Orkin et al publication, reaffirm the teachings of Orkin et al that, even after the two years, there is no evidence of how to use gene therapy to predictably treat any disease (let alone a particular group of diseases, such as cancer as taught by the instant specification). Verma et al teach "Although more than 200 clinical trials are currently underway worldwide, with hundreds of patients enrolled, there is still no single outcome that we can point to as a success story." (page 239, column 1). This reference teaches the considerable hurdles that must be overcome, including making sure that delivery of the gene gets to the right cells and getting enough of the gene delivered (page 239). This reference teaches that "The Achilles heel of gene therapy is gene delivery ... Thus far, the problem has been an inability to deliver genes efficiently and to obtain sustained expression. Most of these approaches suffer from poor efficiency of delivery and transient expression of the gene." (page 236, column 3). This reference also specifically addresses the problems of adenovirus vectors such as transient expression and considerable immunological problems to be overcome (page 241). Verma et al conclude by stating that "We now need a renewed emphasis on the basic science behind gene therapy-particularly the three intertwined fields of vectors, immunology and cell biology. ... Clearly, existing vectors need to be streamlined

further, and vectors that target specific types of cell are being developed." (page 242).

With regard to use of an antisense molecule against NF-kB in the claimed method, it is equally unpredictable how to use it for cancer therapy, like the other types of inhibitors described above. Also, Branch teaches that they have major, unresolved problems such as: they are far more difficult to produce than was originally imagined, their ability to eliminate the function of a single gene has never been proven, a wide variety of unexpected non-antisense effects occur, making it hard to produce drugs that act primarily through true antisense mechanisms and complicate the use of the agents (abstract; throughout the reference).

In view of the large quantity of experimentation necessary to determine the unpredictable parameters necessary for successfully using a cancer treatment based upon the claimed method in vivo, the lack of significant direction or guidance presented, the absence of working examples, the breadth of the claims which includes the treatment of very many, very different cancers, using a wide range of very different NF-kB inhibitors and chemotherapeutic agent combinations, and the unpredictable and undeveloped state of the art with respect to formulating even one of a broad class of different NF-kB inhibitors into a functional drug that can treat cancer in vivo (along with a chemotherapeutic agent), let alone a large number of very

different inhibitors for various very different cancers, it would require undue experimentation for one skilled in the art to practice the claimed invention.

In conclusion, it has been established by the Court that a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion. Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention. It is true that a specification need not disclose what is well known in the art. However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. In the instant case, the applicants toss out a mere germ of an idea of how to use a any NF-kB inhibitor, along with an anticancer drug, to treat any cancer, and then essentially simply state that any administration technique known in the prior art as appropriate be used to practice the invention. However, because of the state and unpredictability of the prior art as evidenced by the cited

references, the prior art cannot be relied upon for teachings of specifically how to practice a cancer therapy method based upon a broad class of compounds (NF-kB inhibitors) for which there are no specific teachings taught on how to use the compounds as a therapeutic in vivo. Thus, the specification must teach how to use the invention, a critical detail in teaching the invention. The specification, without working examples or specific guidance to methods that are known to work for the claimed method in vivo, merely relies upon the generic teachings of the prior art as applied to other therapies that cannot be predictably applied to the instant claimed invention. As described above, because of the failure and unpredictability of the prior cancer and gene therapy arts, the prior art cannot be relied upon for enablement of the claimed methods. Therefore, there is no enabling disclosure of the claimed invention.

Response to Arguments

The applicant's arguments and the Baldwin Declaration under 37 CFR 1.132 filed 4/13/99 is insufficient to overcome the rejection of claims 1-12 (and now extended to new claims 14-28) based upon 35 USC 112, first paragraph, as set forth in the last Office action because of the following reasons.

The applicant argues that the present claims are not directed to a method of curing cancer, but to methods of enhancing the cytotoxic effects of chemotherapeutic agents, and thus act as adjuvants to known chemotherapeutic agents. This argument is not persuasive because all throughout the rejection the reference was to treatment of cancer, not curing. Even the passage that the applicant points to, "... resulting in successful treatment of cancer" is not directed to an argument concerning curing cancer, only that the treatment is successful, i.e. it functions. Cancer treatment which results in the tumor merely shrinking can be considered to be a successful treatment, depending on the cancer type. There was no argument in the rejection directed to the unpredictability of curing cancer because the claims were not directed to that. The main arguments of the rejection were directed to the unpredictability of going from an agent which has in vitro biological activity to translating it into an agent (and administration method) that can be used as claimed, to enhance the cytotoxic effects of another chemotherapeutic agent (i.e., make the chemotherapy more effective compared to the administration of the chemotherapeutic agent by itself). The high unpredictability of anti-cancer drugs which show successful results when tested in nude mice/tumor

models actually being functional in a patient is another major argument. Also, the arguments were directed to the unpredictability of certain types of treatment, such as gene therapy-based methods and anti-sense methods.

The applicant argues that the Office Action's statements regarding the unpredictable nature of drug research are misplaced as applied to newly added claims directed to improvements on existing chemotherapeutic agents because the claims build on the established therapeutic methods. This argument is not persuasive because the unpredictable nature of drug research argument was and is directed to the unpredictability concerning the use of an NF-kB inhibitor itself, or especially in conjunction with another chemotherapeutic agent, not the chemotherapeutic administration part alone. It was presumed that normal prior art teachings of how to use the particular known chemotherapeutic agent that is used in practicing the claimed invention would be used. That type of teaching was not indicated as being unpredictable. The applicant thus has not addressed the main point, that use of the various very different NF-kB inhibitors as claimed is unpredictable as demonstrated by the cited art.

The applicant cites In Re Cortright, which shows that it is error to require curing, when only treatment is taught (and

presumably claimed), and argues that the claims in the instant application are impermissibly interpreted in the rejection as requiring "curing". This argument is not persuasive for the reasons given above. All of the arguments in the rejection are directed to the unpredictability of treatment, not curing. The art cited in the rejection shows the very unpredictable nature of successfully making and using an agent as a treatment based upon its in vitro biological activity or biological activity in a nude mice/cancer model.

With regard to the cited art which shows that nude mice/cancer models are unpredictive for cancer drug discovery, the applicant argues that the present examples are not used to demonstrate an entirely new mechanism for treating cancer, but to show that the present methods improve the effects of known anti-cancer chemotherapeutics. The applicants also refer to two issued US patents which claim methods of treating cancer where no human data was provided and no cures was reported, including '023 which claims an adjuvant treatment. These arguments are not persuasive for the following reasons. The in vivo data that the applicant relies upon is from a nude mice/cancer model which the cited art shows to be specifically very unpredictable for cancer drug discovery. Administration of an NF-kB inhibitor to aid in

the treatment of cancer, even if it is with a known chemotherapeutic agent, still is the use of the NF-kB as a drug to treat cancer. All of the unpredictable factors concerning making drug treatments from compounds which have a promising in vitro biological activity or promising activity in a nude mice/cancer model applies to NF-kB inhibitors because the inhibitors still are drugs that have to operate on the cancer. The applicant has failed to persuasively argue that the cited art showing the unpredictability is incorrect or of little relevance. Thus, although the applicant argues that the claimed invention merely improves the effects of known anti-cancer chemotherapeutics, it does rely on the effects of an NF-kB inhibitor as shown in a model which is unpredictable for cancer drug discovery, and thus it is unpredictable that the NF-kB inhibitor can be used to increase the cytotoxic effects of anti-cancer drugs (and thus as a part of a chemotherapeutic treatment of cancer) in an actual patient. With regard to the arguments drawn to the two issued patents, each application stands on its own merits and thus the fact that two patents were issued which are in the same general area as the instant application, has no real bearing on the merits of the instant case because the

reasons that the two patents were issued are different and are not necessarily present in the instant case.

The applicant argues that the inventors' work has been published in a peer-reviewed journal, reports the use of NF-kB inhibitors in conjunction with a chemotherapeutic agent in a model of colorectal tumors, and thus supports the applicant's claims. The toxicity of systemic TNFa administration is discussed in the reference and the present claims directed to the use of TNFa has been limited to intratumoral administration. The applicant also argues that the article describes the use of NF-kB inhibitors as an adjuvant to chemotherapy. These arguments are not persuasive. The data reported in the reference (and discussed in the Baldwin Declaration) is based upon a nude mice/cancer model which the cited reference teaches is very unpredictable in cancer drug development. The arguments concerning the unpredictability of this model system are discussed above and equally apply to the data described in the Baldwin Declaration. This argument also applies to the TNFa argument. Finally, the argument that the claimed invention is drawn to adjuvant use is also addressed above.

The applicant argues that with regard to gene therapy, only claim 5 recites transformation of a cell to deliver an NF-kB

inhibitor. The applicant states that other methods of delivery such as intratumoral administration are viable options. The applicant argues that the Baldwin Declaration shows additional experiments conducted using the proteasome inhibitor PS-341 in combination with a known antineoplastic agent irinotecan. These arguments are not persuasive for the following reasons. In responding to the arguments concerning the unpredictability of gene therapy, the applicant has failed to convincingly argue why the cited references are incorrect or are not relevant. Alternative administration methods involving transferring a gene into cells in an organism also is considered to be gene therapy which is shown by the cited art to be unpredictable and are as unpredictable in nature as systemic administration, thus the fact that other delivery methods can be tried such as intratumoral administration is not a convincing argument. Additionally, the applicant fails to address the Branch reference which specifically teaches the unpredictability of the use of one class of NF-kB inhibitors, antisense inhibitors.

The applicant argues that although further clinical research will be required before the present methods can be introduced into clinical practice, the Federal Circuit has reiterated that therapeutic utility sufficient under the patent laws should not

be confused with the requirements of the FDA. This is not persuasive because the argument is directed to utility, which only applies to rejections under 35 USC 101, not to the instant rejection which is under 35 USC 112, first paragraph and concerns whether the claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention.

Finally, the applicant argues that the present methods have been shown using both a vector expressing NF-kB inhibitor and using a proteasome inhibitor of NF-kB in an animal model to enhance regression of tumors in animals treated with known chemotherapeutic compounds, and that in view of the record, the applicants believe that the claims are enabled. This is not persuasive because not only has the applicant not convincingly addressed the extreme amounts of unpredictability of making and using the claimed methods for a cancer treatment, as shown by the cited art, but also the applicant has not convincingly and specifically addressed the cited art that shows that the nude mice/cancer model that the applicant puts so much weight on, is highly unpredictable for development of anti-cancer drugs. Therefore, in light of all of the available evidence, including

the rejection set forth above and in the last Office Action, the applicant's arguments, and the arguments set forth above, the claims are still considered to be containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention, and thus the rejection under 35 USC 112, first paragraph is maintained.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee

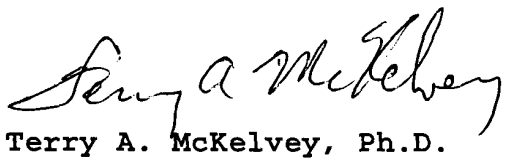
pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Certain papers related to this application may be submitted to Art Unit 1636 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone numbers for the Group are (703) 308-4242 and (703) 305-3014. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Terry A. McKelvey whose telephone number is (703) 305-7213. The examiner can normally be reached on Monday through Friday, except for Wednesdays, from about 6:30 AM to about 5:00 PM. A phone message left at this number will be responded to as soon as possible (usually no later than 24 hours after receipt by the examiner).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. George Elliott, can be reached on (703) 308-4003.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.



Terry A. McKelvey, Ph.D.
Primary Examiner
Art Unit 1636

June 14, 1999